negative experiences appears to be specific to the social domain: participants exposed to endotoxin showed enhanced neural activity in response to threatening stimuli that were social in nature (e.g., angry faces), but not to threatening stimuli that were non-social (e.g., snakes)[6].

Inflammation also increases sensitivity to positive social stimuli. Participants exposed to endotoxin reported having a greater desire to be with their loved ones, and showed enhanced reward-related neural activity to viewing images of their loved ones[7]. Similarly, participants exposed to endotoxin showed greater reward-related neural activity in response to receiving positive feedback from others[5]. These results support the idea that, during states of sickness, it may be adaptive to show increased reward- and approach-related responding to loved ones or to friendly others who could provide help and support. This inflammation-enhanced sensitivity to positive stimuli also seems specific to the social domain, as inflammation actually reduces reward-related neural responding to positive stimuli that are non-social, such as money[8].

Interestingly, the relationship between heightened inflammation and increased sensitivity to social stimuli is reminiscent of what is observed in loneliness, another emerging mental health issue. Lonely individuals show elevated inflammation, an increased sensitivity to negative social experiences, and, just like participants exposed to endotoxin, greater reward-related neural activity in response to viewing images of close others[9].

Thus, loneliness and states of heightened inflammation share the same characteristic pattern of heightened sensitivity to the social world. Building on these overlaps, we are currently examining whether experiences of loneliness and the corresponding enhanced social sensitivity can be reduced through an over-the-counter non-steroidal anti-inflammatory drug.

Altogether, these findings advocate for a stronger consideration of the role of inflammation in psychiatric disorders that involve altered social sensitivity. For instance, while not all forms of depression are inflammatory in nature, it is possible that inflammatory-related depression could be distinguished from non-inflammatory depression by a characteristic increase in reward-related neural activity to close others. Distinguishing between these forms of depression might help to better inform treatment strategies (e.g., anti-inflammatory drugs vs. cognitive-behavioral therapy).

Moreover, these findings also suggest a stronger consideration of the mental health consequences of inflammatory diseases. Those who have chronic inflammatory disorders may be at a greater risk for enhanced social sensitivities, which may put them at a higher risk for loneliness and depression, and may increase the strain placed on their social relationships.

Appreciating the intimate links between the immune system and social behavior may provide a new perspective from which to understand and treat mental health issues.

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The synaptic pruning hypothesis of schizophrenia: promises and challenges

Schizophrenia is widely considered a neurodevelopmental disorder, as suggested by its typical onset in adolescence and young adulthood, neurocognitive and social impairments preceding onset, and neuropathologic alterations of aberrant cellular organization, decreased neuronal volume, and dendritic spine loss.

Recent genome-wide association studies in large samples have revealed 108 genetic loci significantly associated with the risk of the disorder. The strongest risk was repeatedly identified in the major histocompatibility complex, a region rich with immune system genes and complex linkage disequilibrium patterns. Later studies determined that part of the variance for risk arises from the complement component 4 (C4) gene[1].

The complement system is involved in both immunological and regenerative processes, which include dampening inflammatory activation, angiogenesis, apoptotic cell removal, wound healing, and stem cell mobilization. In the central nervous system, complement factors play a role in synaptic pruning that may involve phagocytosis of redundant (or ineffective) synapses as well as enhanced pro-inflammatory cytokine secretion by glial cells inducing neuronal damage and death[2].

Exposure to maternal complement protein during pregnancy may be a risk factor for the development of schizophrenia in offspring[3]. Sellgren et al[4] used a reprogrammed in vitro model of microglia-mediated synapse engulfment and demonstrated increased synapse elimination in schizophrenia patient-derived neural cultures and isolated synaptosomes. Some of this effect was accounted for by carriers of schizophrenia risk-associated variants within the C4 locus.

All of these observations fit nicely into an early model original-

ly suggested by I. Feinberg, who postulated aberrant peri-adolescent pruning of synapses (resulting in either too much or too little pruning) as underlying schizophrenia[5]. In a subsequent paper, we suggested that an exaggerated pruning of synapses during adolescence/young adulthood could explain the onset of the disorder at that age[6]. This view is indirectly supported by phosphorus magnetic resonance spectroscopy studies that showed greater neuropil contraction in first episode schizophrenia[7], which was associated with a gene-dosage effect of C4A and C4B copy numbers[8].

While these observations may help connect several previously murky "dots" in our understanding of the pathophysiology of schizophrenia, several caveats are worth considering. First, the pathophysiology of schizophrenia may not simply be related to synapse loss. Substantive evidence show that abnormalities in myelin, neurons, oligodendrocytes, astrocytes and endothelial cells may also be involved. Human post-mortem studies that demonstrated dendritic spine loss, a proxy measure of synaptic pruning, are primarily localized to the basilar dendrites in the deeper layers of cortex, but not the entire cortex. Second, complement cascade alterations may not be unique to schizophrenia, with recent observations suggesting similar pathophysiological mechanisms in Alzheimer's disease and bipolar disorder.

Third, genetic factors underlying C4 expression may be only one among several possible mechanisms underlying alterations in synaptic pruning. Environmental factors, including intrauterine infections, may lead to complement and inflammatory alterations via maternal immune activation. Sleep deprivation may lead to synapse elimination via microglial phagocytosis. Traumatic brain injury could result in immune and complement activation with loss of synapses. Other genetic factors besides complement component genes affect synaptic pruning, such as genes that code for gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors (all of which are implicated in risk for schizophrenia). Furthermore, OTX2, which is associated with risk for bipolar disorder, impacts timing of synapse elimination via peri-neuronal nets.

Fourth, while complement alterations may be a useful starting point in understanding the schizophrenia puzzle, we are far from developing actionable biomarkers. Peripheral alterations in complement proteins are inconsistently seen, and vary across illness phases. Further, peripheral complement proteins do not cross the intact blood-brain barrier, and are not a proxy for complement activity in the brain. However, activated complement factors may lead to blood-brain barrier dysfunction which may further affect the progression of disease. Thus, future studies also need to examine cerebrospinal fluid samples, across prodromal, early and chronic psychotic states.

Finally, innovative studies are needed to directly demonstrate increased pruning in schizophrenia. Recent observations using a unique ligand for synaptic vesicle glycoprotein-2 showed reduced binding in schizophrenia that is interpreted as reduced synapse density[9]. These findings are awaiting replication.

Thus, many paths may lead to the hypothesized excess of synaptic pruning, and complement abnormalities may be only one such path. Further, accelerated synaptic pruning may be only one of many mechanisms underlying what we call schizophrenia, may not be unique to this illness, and may not be central to this collection of disease entities. The etiopathology of schizophrenia and related disorders is best conquered piecemeal (i.e., by identifying pathophysiologically distinct transdiagnostic subtypes, given their daunting heterogeneity). While the synaptic pruning model may be a promising step in the right direction, there are miles to go before we rest in this pursuit, and many more promises to keep.

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Gut microbiota: a missing link in psychiatry

The gut microbiota consists of the collection of microbes within the intestine, previously considered of little influence from a mental health perspective, but now regarded as a "virtual organ" weighing up to 1.5 kg in the adult intestine and producing molecules of primary importance for brain function and psychological well-being[1].

There are more bacteria in the human intestine than there are human cells in the body, and we feed these bacteria, while in turn they play a fundamental role in maintaining our overall health. The large intestine functions like a fermenter producing a variety of molecules, including most common neurotransmitters such as gamma-aminobutyric acid (GABA) and serotonin, the serotonin precursor tryptophan, and the short chain fatty acids butyrate, propionate and acetate[2].

There are a variety of mechanisms enabling the gut microbes to communicate with the brain. These include the vagus nerve, short chain fatty acids, tryptophan and cytokines[3]. Certain microbes can only act centrally when the vagus nerve is intact, and can no longer do so following vagotomy. Previously, tryptophan was viewed as entirely of dietary origin, while now it has been es-